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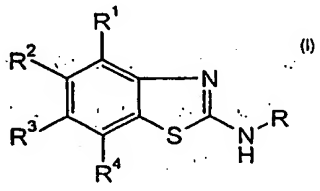
(54) Title: CYCLIZATION PROCESS FOR SUBSTITUTED BENZOTHIAZOLE DERIVATIVES



(I)

(57) Abstract: The present invention relates to a process for preparation of amino substituted benzothiazole derivatives of formula (I), wherein R^1, R^2 and R^3 are independently from each other hydrogen, lower alkyl, lower alkoxy or halogen; R^4 is hydrogen, lower alkyl, lower alkyloxy, halogen, or is a five or six membered non aromatic heterocyclyl group, unsubstituted or substituted by lower alkyl or an oxo-group, or is $-NR^5R^6$ wherein R^5 and R^6 are independently from each other hydrogen, lower alkyl, -C(O)-lower alkyl, $-(CH_2)_nO$-lower alkyl or benzyl, opionally substituted by lower alkyl, or is an five or six membered heteroaryl group; R^1 and R^2 or R^2 and R^3 may form together with the corresponding carbon atoms a ring containing $-O-CH_2-O-$ or $-CH=CH-CH=CH-$; R is hydrogen or -C(O)R'; R' is a five or six membered non aromatic heterocyclyl group, five or six membered heteroaryl group or is aryl, which rings may be substituted by the groups, selected from lower alkyl, halogen-lower alkyl, lower alkoxy, cyano, nitro, -C(O)H, -C(O)OH or by pyrrolidin-1-yl-methyl; n is 1 to 4; and to their pharmaceutically acceptable salts, wherein the cyclization is carried out by the treatment of a compound of formula with sulphoxide/HBr/solvent to give the desired products of formula (I) for R is hydrogen (formula IA) and for R is -C(O)R' (formula IB).

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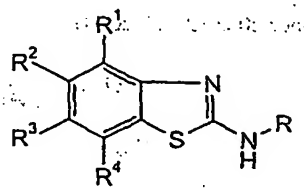
Cyclization process for substituted benzothiazole derivatives

The present invention relates to an improved cyclization process for the preparation of benzothiazoles of formula



I

wherein

R^1, R^2 and R^3 are independently from each other hydrogen, lower alkyl, lower alkoxy or halogen;

R^4 is hydrogen, lower alkyl, lower alkyloxy, halogen, or is a five or six membered non aromatic heterocyclyl group, unsubstituted or substituted by lower alkyl or an oxo-group, or is $-NR^5R^6$, wherein R^5 and R^5 are independently from each other hydrogen, lower alkyl, -C(O)-lower alkyl, $-(CH_2)_nO$-lower alkyl or benzyl, opionally substituted by lower alkyl, or is a five or six membered heteroaryl group;

R^1 and R^2 or R^2 and R^3 may form together with the corresponding carbon atoms a ring containing $-O-CH_2-O-$ or $-CH=CH-CH=CH-$;

R is hydrogen or $-C(O)R'$;

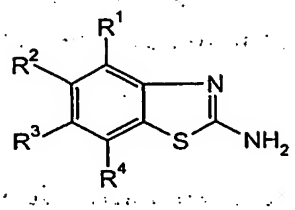
R' is a five or six membered non aromatic heterocyclyl group, five or six membered heteroaryl group or is aryl, which rings may be substituted by the groups, selected from lower alkyl, halogen-lower alkyl, lower alkoxy, cyano, nitro, -C(O)H, -C(O)OH or by pyrrolidin-1-yl-methyl;

n is 1 to 4;

and to their pharmaceutically acceptable salts.

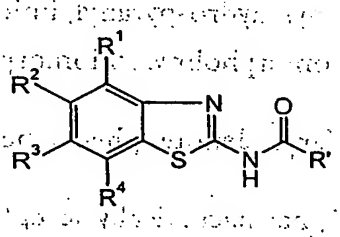
The compounds of formula I are known compounds, described in WO 01/97786.

The object of the present invention is a cyclization process for the preparation of benzothiazole derivatives of formula I for R = hydrogen (formula IA) and for R = -C(O)R' (formula IB), in good yields and with minimal sideproducts.



IA

or



IB

The compounds of formula IA may be used as intermediates for the preparation of compounds of formula IB, which compounds are pharmaceutically active as adenosine receptor ligands.

They are important in the regulation of many aspects of cellular metabolism and in the modulation of different central nervous system activities. The compounds of formula IB may be used in the control or prevention of illnesses based on the modulation of the adenosine system, such as Alzheimer's disease, Parkinson's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse. Furthermore, compounds of the present invention may be useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardioprotective agents. The most preferred indications in accordance with the present invention are those, which base on the A_{2A} receptor antagonistic activity and which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders, neuroprotection and Parkinson's disease. The compounds are further useful in the treatment of diabetes mellitus, obesity and ADHD (attention deficit hyperactivity disorder).

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred lower alkyl groups are groups with 1 - 4 carbon atoms.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "lower alkoxy" denotes a group wherein the alkyl residues are as defined above, and which is attached via an oxygen atom.

The term "five or six membered heteroaryl" denotes the following group: pyrrol-1-yl, tetrazolyl, imidazol-1 or 2-yl, pyrazol1-yl, pyridin-1, 2, 3 or 4–yl, pyrazinyl, pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl, thienyl or furyl;

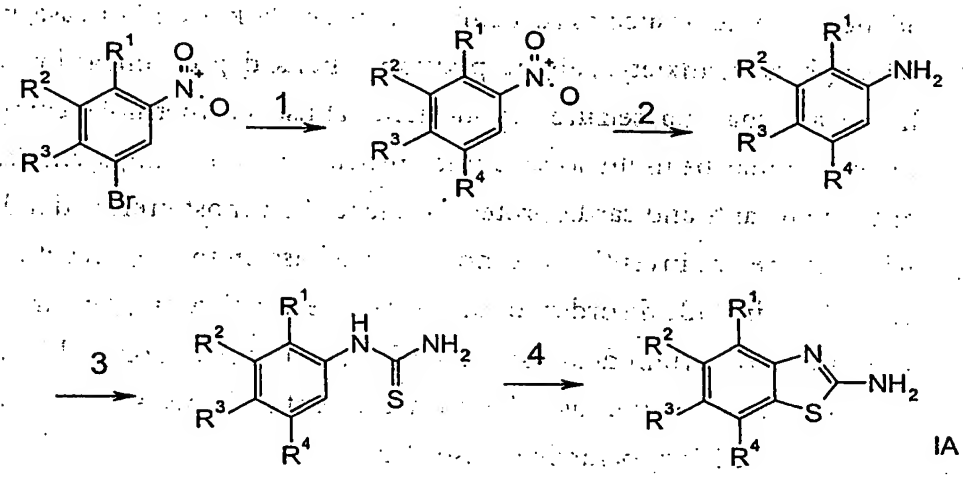
The term "five or six membered non aromatic heterocyclyl" denotes the following groups: pyrrolidinyl, hydro-pyranyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiomorpholin-1,1-dioxo or thiomorpholin-1-oxo.

The term "aryl" denotes phenyl, benzyl or naphthyl.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

In general, the preparation of compounds of formula I, wherein R is hydrogen, is well known. For example, in WO 01/97786 the following process is described:

Scheme 1



IA

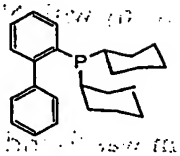
wherein the numbers 1 – 4 have the following meaning:

1 HR^4, $Pd(OAc)_2$, BDCP, K_3PO_4, DME (ethylene glycol dimethyl ether), 80 °C/24h/90 %;

2 H_2, Pd-C, $EtOH/CH_2Cl_2$, RT/12h/95 %;

3 PhCONCS, acetone, RT/30min/95 % and NaOMe, MeOH, RT/2h/90 %;

4 $SOCl_2$, 55 °C/10min/75 %;



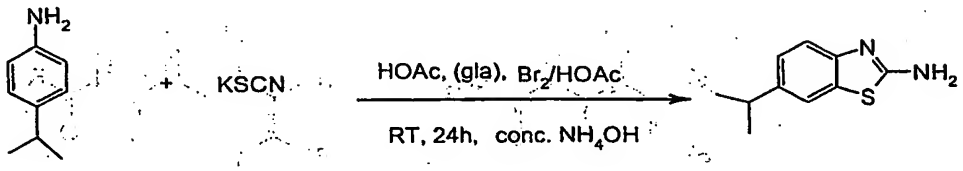
BDCP is

The definition of substituents is described above.

It has been shown that most of starting marterials and the ligand are very expensive and only available in small quantities, and the cyclization step could not be scaled up without resorting to chromatography.

Another way to amino-benzothiazoles is described in EP 282971 as follows:

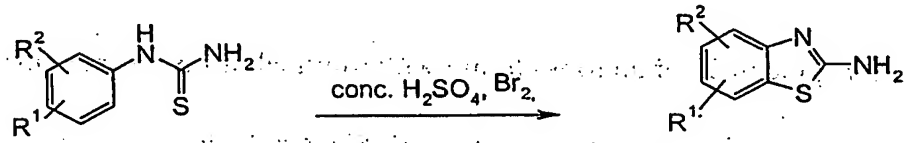
Scheme 2



It has been shown that this reaction step often leads to amino-benzothiazoles in low yields due to competing reactions.

EP 529 600 describes a process for preparation of amino-benzothiazoles comprising the following step:

Scheme 3



It has been shown that the reaction variants, conducted according to literature precedent, such as $Br_2/CHCl_3$ or AcOH, I_2/MeOH or $SOCl_2/CHCl_3$ are often not suitable for the preparation of amino-benzothiazoles, especially in large amounts.

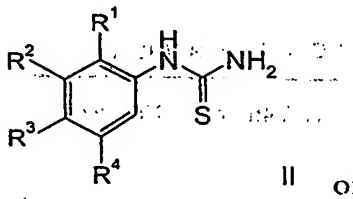
Due to the relative high electron density within the amino-substituted phenyl ring in some specific cases required for the present purposes, competing reactions on this ring before or after cyclization always occurred to a certain extents. Other approaches such as the use of

aq NH_4Br and H_2SO_4 (EP 529600) or treating the aniline directly with $NaSCN/Br_2$/ AcOH (*Synthesis, 970, 31, 2000*) failed to offer any improvement.

A more subtle way of activating the thione sulphur atom was found in the acid catalyzed transfer oxidation of thioureas with DMSO (*J. Heterocyclic Chem., 63, 37, 2000*). But in the absence of suitable trapping agents a dimerization reaction took place to give undesired iminothiadiazoles.

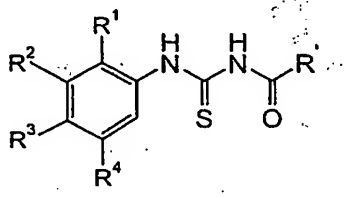
All methods, described in the literature, do not give the desired end products of formula IA and IB in good yields without unpredictable side products.

In order to overcome this problem, it has been found that the treatment of compounds of formulas



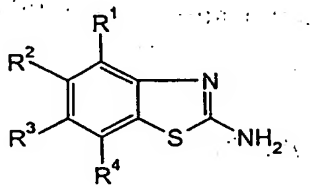
II

or



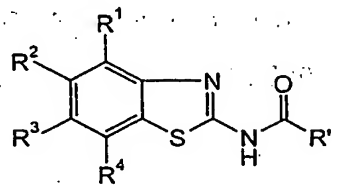
III

with sulphoxide/HBr/solvent gave the desired products of formulas



I A

or



IB

in a good yield of up to 90 % and with minimal or no side reactions.

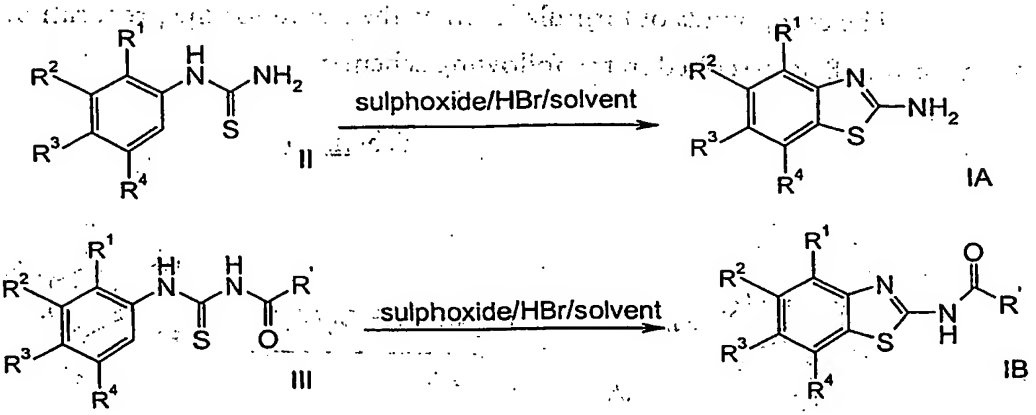
As a sulphoxide, for example, DMSO is suitable, since it is commercially available, cheap and non-toxic.

HBr may be used in any form, including gaseous, or for example in form of an *in situ* prepared bromide salt and a strong acid. Suitable is HBr-AcOH, since this represents a convenient form of 'liquid' concentrated HBr.

As a solvent may be used, for example, CH_2Cl_2, CH_3CN, THF, AcOH or EtOAc. Preferred solvents are AcOH or EtOAc.

In more detail, the reactions may be described as follows:

Scheme 4



A thiourea of formula II or III is suspended with vigorous stirring in ethyl acetate (EtOAc) at 80 °C. Hydrogen bromide (HBr = 33 %) in acetic acid is added dropwise within 0.2 h, followed by the addition of dimethylsulfoxide in one portion. The suspension is refluxed for 4 h. Then the reaction mixture is cooled to RT and after 0.2 h is filtered. The product is washed portionwise with ethyl acetate. The aminobenzothiazole IA or the corresponding benzamide of formula IB is then purified by liberating it from the crude HBr-salt. This is dissolved in ethanol, diluted with water and heated to 55 °C. The obtained solution is basified with aqueous ammonia to pH 9-10, forming a suspension which is stirred and allowed to cool to RT overnight (16 h). The products are filtered and washed portionwise with aqueous ethanol and then dried for 24 h at 45 °C. Yield ~90 %.

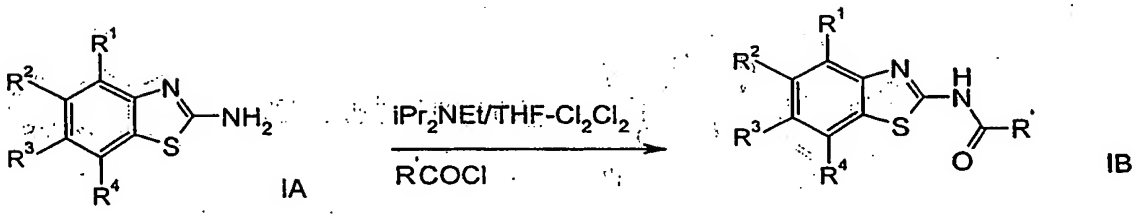
Furthermore, it has been shown that the treatment of a thiourea of formulas II or III with DMSO/HBr/AcOH delivered the desired product of formula IA or IB (yield: ~60 – 80 %), but always accompanied by unpredictable amounts of iminothiazoles (~5 – 25 %). The formation of the side product was attributed to the partial solubility of the protonated thioureas of formula II or III in hot AcOH. Aqueous HBr was also effective, but induced some thiourea-urea transformation. Two equivalents of HBr was necessary for complete conversion in the cases where a basic unit was attached to the aryl-ring. The reaction proceeded best at >70 °C, but was rapid and fairly exothermic at this temperature. The starting material quickly dissolved upon DMSO addition and the product almost completely precipitated immediately thereafter.

It has been found that after cooling and filtration, the benzothiazoles of formulas IA or IB may be isolated in good purity. By conducting the reaction entirely in EtOAc, the

problem of competitive dimerization was finally overcome since the HBr-salts of both reactant and product were barely soluble in this solvent thus averting all further side reactions.

The compounds of formula IA may then used for the preparation of end-products of formula IB as described in the following scheme:

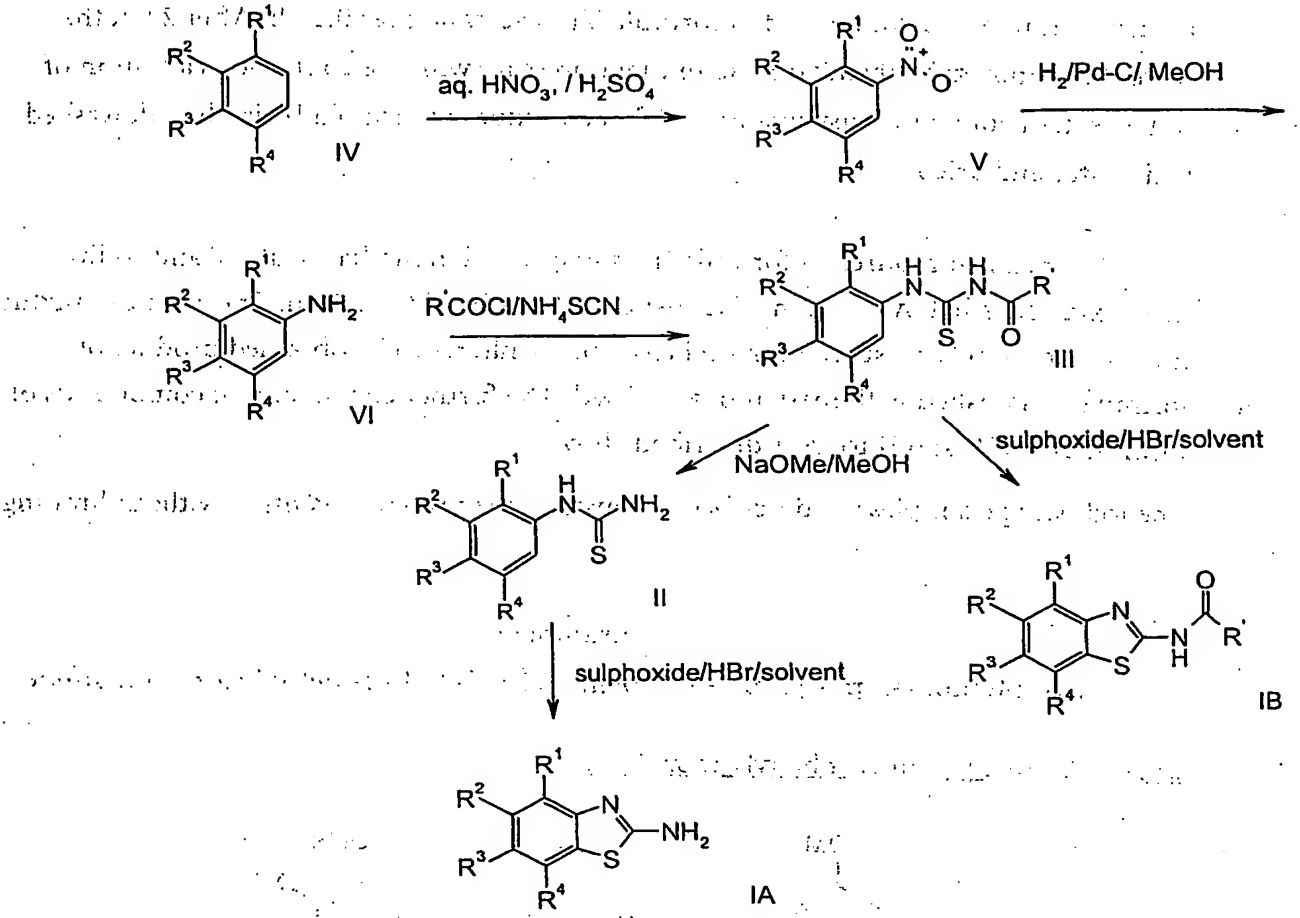
Scheme 5



This reaction is described in more detail in WO 01/97786.

The starting compounds of formulas II and III may be prepared as described in the above scheme:

Scheme 6



Compounds of formula III may be prepared as follows:

A compound of formula IV is dissolved in sulphuric acid, maintaining a temperature between 0-10 °C. The obtained solution is cooled to ca. –5 °C. In a separate flask, nitric acid is added to sulphuric acid and precooled to ca. 10 °C. This mixture is then added the above solution within 1 h ensuring that the temperature remained <0 °C. The reaction mixture is quenched into ice and to the aqueous solution aqueous ammonia is added. The suspension is diluted with water and stirred at RT for 0.2 h before being filtered. The obtained product of formula V is washed with water and dried. This compound is then suspended in methanol and dichloromethane is added to generate a solution. Pd-C is added and the reduction is commenced at RT under hydrogen with stirring. The reaction is complete after 1.5 h. The mixture is filtered, the residue is rinsed with MeOH and the filtrate is concentrated under reduced pressure. Water is added and the resulting suspension is heated again to 60 °C to remove residual MeOH. The obtained product of formula VI is filtered, washed with aqueous MeOH and dried.

Ammonium thiocyanate is dissolved in acetone at RT and benzoyl chloride is added to create PhCONCS *in situ*. The reaction mixture is heated to reflux and then treated with a warm solution of a compound of formula VI in acetone over 0.25 h. After 2.5h, the solvent is removed by distillation at ambient pressure with the continuous addition of water. After cooling the suspension to RT, the product of formula III is filtered, washed with water and dried.

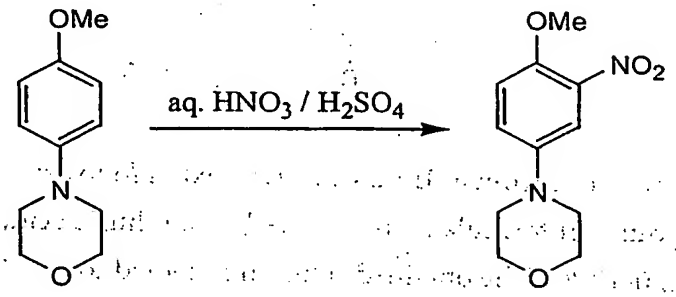
The benzoylthiourea of formula III is suspended in methanol at RT and sodium methoxide is added over 0.75 h. The suspension is stirred for 2.75 h. The reaction mixture is cooled to ~0 °C and stirred for 1 h before being filtered. The obtained product of formula II is washed with methanol and dried. The further conversion of compounds of formula III to IB and II to IA is described above.

The following examples are described to illustrate the present invention without limiting it:

Example 1

N-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-2-methyl-isonicotinamide

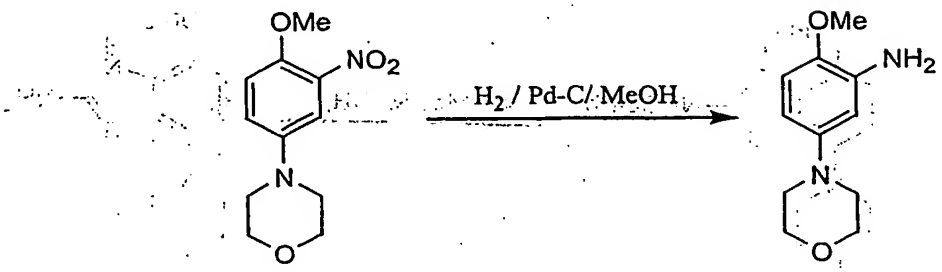
a) 4-(4-Methoxy-3-nitro-phenyl)-morpholine



60.0 g Arylmorpholine (0.31 mol) were dissolved in 273 ml 95 % sulphuric acid (4.84 mol, 15.6 eq.), while maintaining a temperature between 0-10 °C. Stirring at 10 °C was continued for 0.5 h to produce a brown solution which was cooled to ca. –5 °C. In a separate flask, 20.9 ml 65 % nitric acid (0.34 mol, 0.98 eq.) were added to 30 ml 95 % sulphuric acid (0.53 mol, 1.7 eq) precooled to ca. 10 °C. This nitrating mixture was then added to the above solution within 1 h ensuring that the temperature remained <0 °C. The dark brown reaction mixture was then worked up in a conventional manner (70 g, ~95 %).

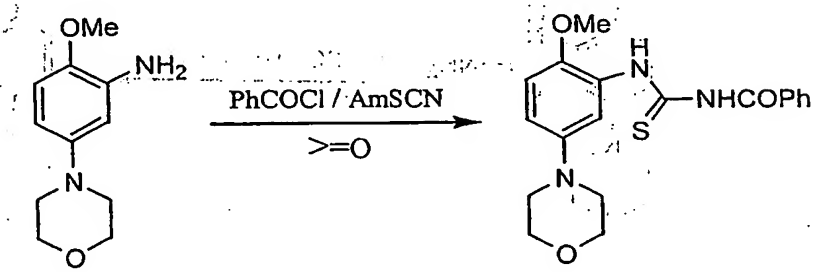
The crude product was sufficiently pure to be used directly in the next step.

b) 2-Methoxy-5-morpholin-4-yl-phenylamine



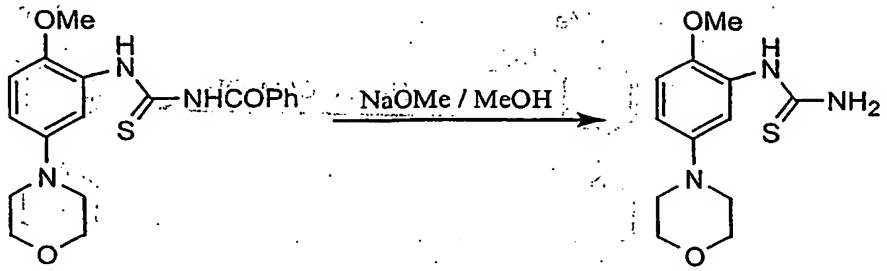
40.2 g Nitroanisole (0.169 mmol) were suspended in 402 ml methanol and 65 ml dichloromethane were added to generate a solution. 2.0 g 5 % Pd-C were added and the reduction was commenced at RT under hydrogen. The reaction was complete after 1.5 h. The reaction mixture was then worked up in a conventional manner. The crude product was sufficiently pure to be used directly in the next step.
32.8 g (93 %).

c) 1-Benzoyl-3-(2-methoxy-5-morpholin-4-yl-phenyl)-thiourea



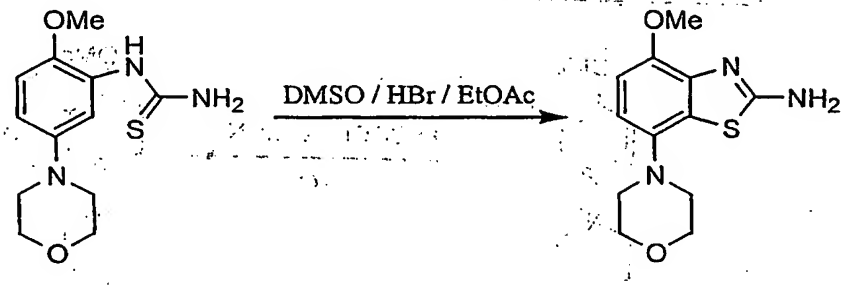
13.1 g Ammonium thiocyanate (AmSCN) (142 mmol, 1.1 eq.) were dissolved in 135 ml acetone at RT. 22.7 g Benzoyl chloride (160 mmol, 1.02 eq.) were added in one portion. The reaction mixture was heated to reflux (~60 °C) for 0.5 h and then treated with a warm (~40 °C) solution of 32.5 g the aniline (156 mmol) in 260 ml acetone over 0.25 h. The heating was continued for 2.5 h. The work-up was carried out in conventional manner. The crude product was sufficiently pure to be used directly in the next step. 54.8 g (94 %).

d) (2-Methoxy-5-morpholin-4-yl-phenyl)-thiourea



212 g Benzoylthiourea (571 mmol) were suspended in 1270 ml methanol at RT and 155 ml 30 % methanolic sodium methoxide (861 mmol, 1.5 eq.) were added over 0.75 h. The suspension was stirred for 2.75 h, cooled to ~0 °C and stirred for 1 h before being filtered. The crude product was sufficiently pure to be used directly in the next step.
148.7 g (97 %).

e) 4-Methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine



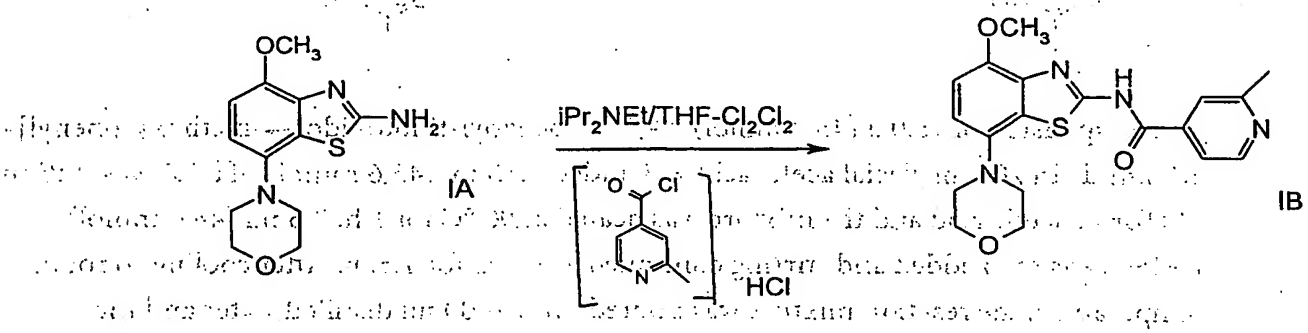
50 g (187 mmol) thiourea were suspended with vigorous stirring in 560 ml ethyl acetate. The light grey suspension was brought to reflux and 1.8 g hydrogen bromide (33 % in acetic acid, 65.5 ml, 374 mmol, 2.0 eq.) were added dropwise within 0.2 h, followed by, 0.2 h later, 17.5 g dimethylsulfoxide (224 mmol, 15.9 ml, 1.2 eq.) in one portion. The suspension was refluxed for 4 h during which the colour changed from dark to light yellow. The reaction mixture was cooled to RT and after 0.2 h was filtered. The product was washed portionwise with 190 ml ethyl acetate. The aminobenzothiazole was purified by liberating it from the undried crude HBr-salt. This was dissolved in 450 ml ethanol, diluted with 600 ml water and heated to 55 °C. The red solution was basified with 50 ml 25 % aqueous ammonia to pH 9-10, forming a suspension which was stirred and allowed to cool to RT overnight (16 h). The product was filtered and washed portionwise with 140 ml 50 % aqueous ethanol and then dried for 24 h at 45 °C/1 mb.
45.1 g (90 %)

^{1}H-NMR: (400 MHz, $CDCl_3$): δ = 3.05 (m, 4H), 3.86 (m, 4H), 3.95 (s, 3H), 5.14 (bs, 2H),

6.73 (d, 2H), 6.78 (d, 2H).

MS: 266 ($M + H^+$).

f) N-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-2-methyl-isonicotinamide

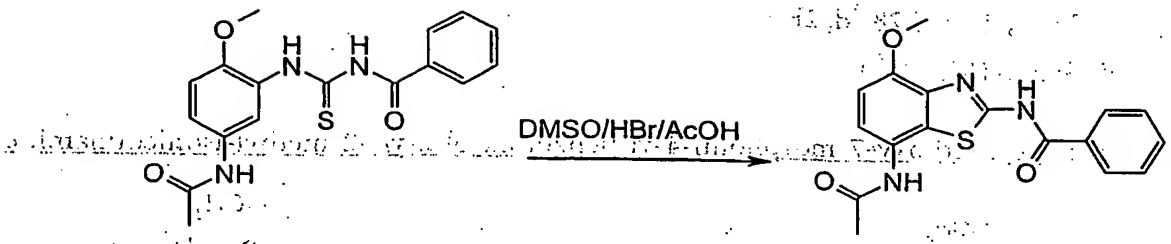


20.0 g Pyridine acid (115 mmol) were suspended at RT in 100 ml dichloromethane. 0.5 ml Dimethylformamide (6.5 mmol) was added and after 0.2 h, 14.9 g oxalyl chloride (10.2 ml, 115 mmol) were added over 2 min. The dropping funnel was rinsed with 4 ml dichloromethane. The brown suspension was stirred at RT for 3 h. Then 200 ml tetrahydrofuran were added causing the acid chloride to partially precipitate. After 0.2h, 24.3 g aminobenzothiazole (IA) (92 mmol) were added in one portion at RT. Directly afterwards, 56.0 ml N-ethyldiisopropylamine (42 g, 321 mmol) were added over 0.1 h. and the reaction mixture was stirred at RT overnight (~17 h). The contents were heated to reflux (~60 °C) and 300 ml water were added whilst maintaining ca. constant volume throughout a distillation process until the internal temperature reached 90 °C. Once all the water was added, heating was increased to 110 °C and a total of 280 ml of distillate was collected. A further 320 ml water was added in one portion and the temperature was increased to 120 °C whereby the internal and distillate temperature rose to ~70 °C. Around 20 ml more solvent was removed and after 0.1 h, the internal and distillate temperatures reached 90 ° and 75 °C respectively. The reaction contents were allowed to cool to RT (ca. 1.2 h) then stirring was continued for 1.5 h to complete the precipitation of the product. This was filtered and washed in 30 ml portions with a total of 150 ml water. Further purification was carried out in conventional manner.

Yield: 30.4 g (86 % from amine).

Example 2

N-(7-Acetylamino-4-methoxy-benzothiazol-2-yl)-benzamide

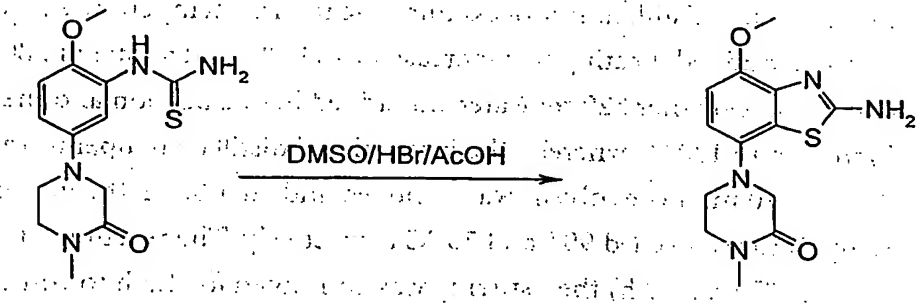


To a suspension of 15.0 g (43.7 mmol) *N*-[3-(3-benzoyl-thioureido)-4-methoxy-phenyl]-acetamide in 200 ml glacial acetic acid was added 7.65 ml (43.6 mmol) of a 5.7 M solution of HBr in acetic acid and the mixture was heated at 90 °C for 1 h. 2.5 ml (48.0 mmol) DMSO was then added and stirring continued at 90 °C for 1.5. h. After cooling to room temperature, the reaction mixture was poured onto 1000 ml distilled water and the resulting slurry stirred for 15 min. The mixture was then filtered, and the filter cake washed with water, then dried *in vacuo* at 50 °C affording 12.8 g (86 %) *N*-(7-acetylamino-4-methoxy-benzothiazol-2-yl)-benzamide as a light brown solid. ES-MS m/e (%): 342 ($M+H^+$, 100).

In an analogous manner there were obtained:

Example 3

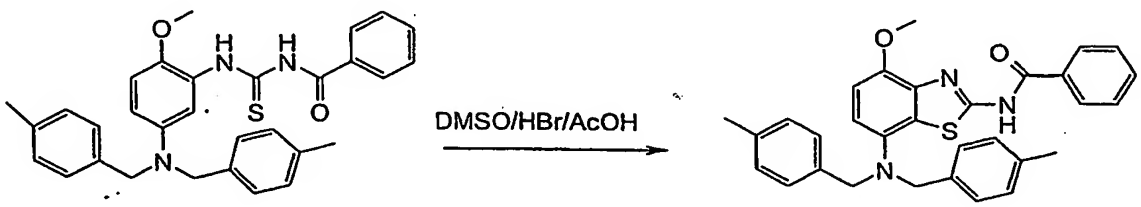
4-(2-Amino-4-methoxy-benzothiazol-7-yl)-1-methyl-piperazin-2-one



From [2-methoxy-5-(4-methyl-3-oxo-piperazin-1-yl)-phenyl]-thiourea with HBr-AcOH (4 equiv.) and DMSO (2.4 equiv.) in AcOH. ES-MS m/e (%): 293 ($M+H^+$, 100).

Example 4

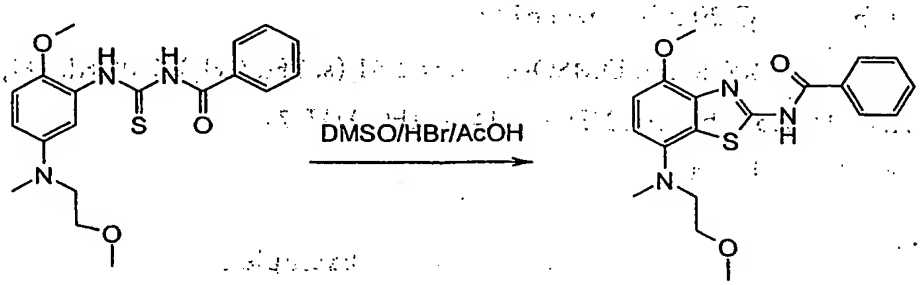
N-{7-[Bis-(4-methyl-benzyl)-amino]-4-methoxy-benzothiazol-2-yl}-benzamide



From 1-benzoyl-3-{5-[bis-(4-methyl-benzyl)-amino]-2-methoxy-phenyl}-thiourea with HBr-AcOH (2 equiv.) and DMSO (1.1 equiv.) in AcOH.
ES-MS m/e (%): 508 ($M+H^+$, 100).

Example 5

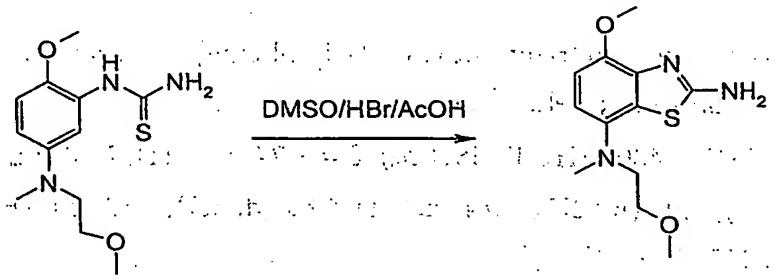
N-{4-Methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide



From 1-benzoyl-3-{2-methoxy-5-[(2-methoxy-ethyl)-methyl-amino]-phenyl}-thiourea with HBr-AcOH (2 equiv.) and DMSO (1.1 equiv.) in AcOH.
ES-MS m/e (%): 372 ($M+H^+$, 100).

Example 6

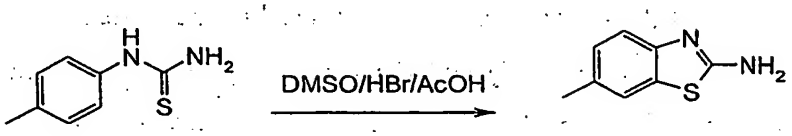
4-Methoxy-*N*7-(2-methoxy-ethyl)-*N*7-methyl-benzothiazole-2,7-diamine



From {2-methoxy-5-[(2-methoxy-ethyl)-methyl-amino]-phenyl}-thiourea with HBr-AcOH (2 equiv.) and DMSO (1.1 equiv.) in AcOH.
ES-MS m/e (%): 268 ($M+H^+$, 100).

Example 7

2-Amino-6-methyl-benzothiazole



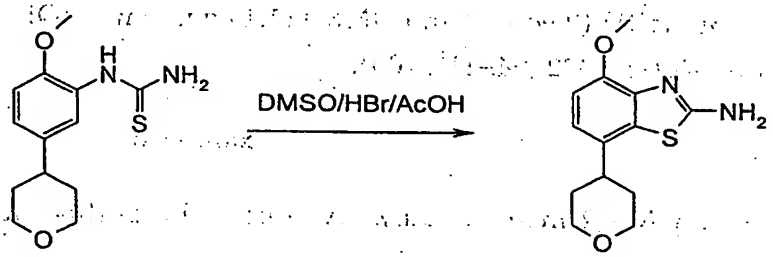
(4-Methylphenyl)thiourea (2 mmol) was added to AcOH (4 ml) and the suspension was heated to 80 °C. To the solution formed was added 33 % HBr in AcOH (4 mmol) followed by DMSO (2.1 mmol). After stirring at 80 °C for1 h, the reaction mixture was cooled to 50 °C, diluted with EtOAc (10 ml) and filtered. The product (as HBr-salt) was taken up in H_2O (5 ml) and treated with 1M aq. $NaHCO_3$ (2 ml). Stirring was continued for 0.2 h, the precipitated aminobenzothiazole was then filtered, washed with H_2O (10 ml) and dried (16h at 45 °C/20 mb); yield 67 %.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.31 (s, 3H, CH_3), 7.00 (d, 1H, ArH-5), 7.21 (d, 1H, ArH-4), 7.31 (bs, 2H, NH_2), 7.44 (s, 1H, ArH-7).

MS: 165 ($M + H^+$).

Example 8

4-Methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-ylamine



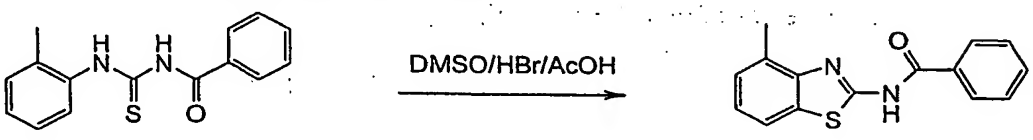
[2-Methoxy-5-(tetrahydropyran-4-yl)-phenyl]-thiourea was treated in the same manner as in Example 7; yield 64 %.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ = 1.74 (m, 4H), 2.68 (m, 1H), 3.45 (m, 2H), 3.82 (s, 3H), 3.95 (m, 2H), 6.84 (d, 2H), 6.89 (d, 2H), 7.62 (bs, 1H).

MS: 265 ($M + H^+$).

Example 9

N-(4-Methyl-benzothiazol-2-yl)-benzamide



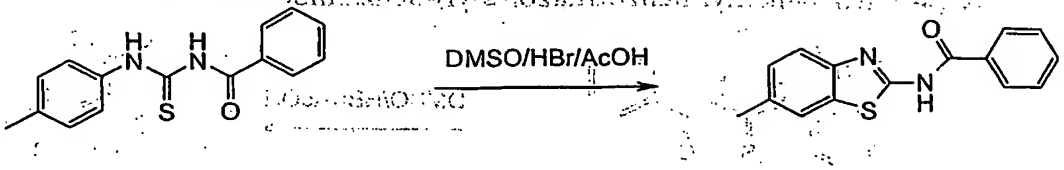
1-Benzoyl-3-o-tolyl-thiourea was treated in the same manner as in Example 7; yield 52 %.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.64 (s, 3H, CH_3), 7.26 (m, 2H), 7.57 (m, 2H), 7.67 (m, 1H), 7.83 (dd, 1H), 8.15 (dd, 1H), 12.9 (bs, 1H).

MS: 269 ($M + H^+$).

Example 10

N-(6-Methyl-benzothiazol-2-yl)-benzamide



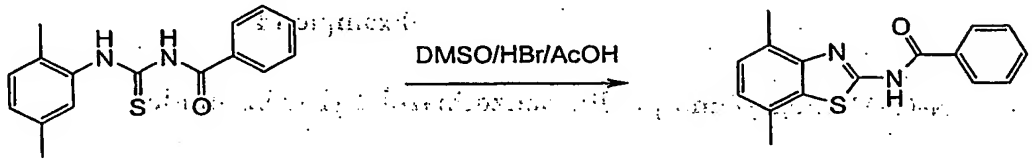
1-Benzoyl-3-p-tolyl-thiourea was treated in the same manner as in Example 7; yield 37 %.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.44 (s, 3H, CH_3), 7.29 (dd, 1H), 7.57 (m, 2H), 7.67 (m, 2H), 7.81 (d, 1H), 8.13 (m, 2H), 12.7 (bs, 1H).

MS: 269 ($M + H^+$).

Example 11

N-(4,7-Dimethyl-benzothiazol-2-yl)-benzamide

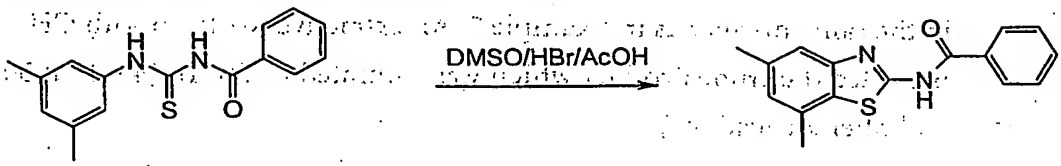


1-Benzoyl-3-(2,5-dimethyl-phenyl)-thiourea was treated in the same manner as in Example 7; yield 76 %.

MS: 283 ($M + H^+$).

Example 12

N-(5,7-Dimethyl-benzothiazol-2-yl)-benzamide

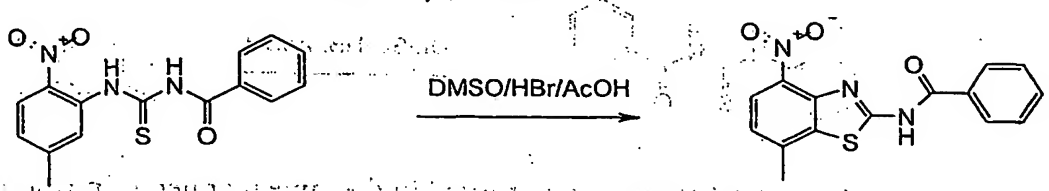


1-Benzoyl-3-(3,5-dimethyl-phenyl)-thiourea was treated in the same manner as in Example 7; yield 83 %.

MS: 283 ($M + H^+$).

Example 13

N-(4-Nitro-7-methyl-benzothiazol-2-yl)-benzamide



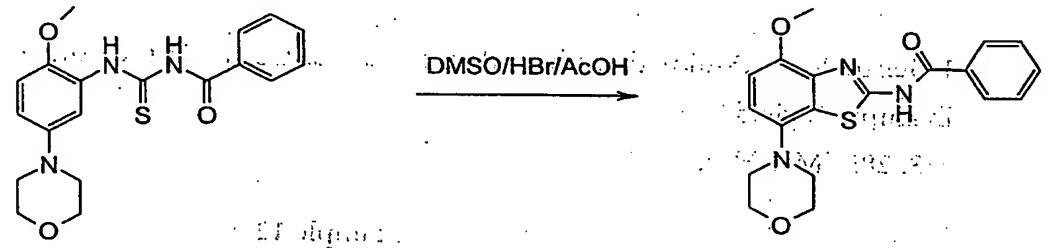
1-(2-Nitro-5-methyl-phenyl)-3-benzoyl-thiourea was treated in the same manner as in Example 7; yield 34 %.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.67 (s, 3H, CH_3), 7.36 (d, 1H), 7.59 (m, 2H), 7.70 (m, 1H), 8.14 (d, 1H), 8.18 (m, 2H), 13.4 (bs, 1H).

MS: 314 ($M + H^+$), 336 ($M + Na^+$).

Example 14

N-(4-Methoxy-7-morpholin-benzothiazol-2-yl)-benzamide



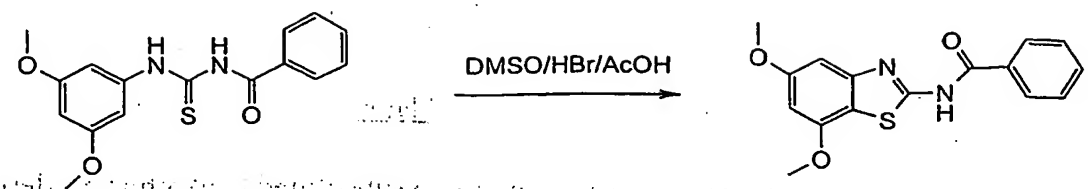
1-Benzoyl-3-(2-methoxy-5-morpholin-4-yl-phenyl)-thiourea was treated in CH_2Cl_2 (5 ml) in the same manner as in Example 7. An extractive work-up with CH_2Cl_2/aq. $NaHCO_3$ provided the crude product which was triturated in TBME (4 ml) at 50 °C, cooled to RT and filtered; yield 68 %.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ = 3.08 (m, 4H), 3.80 (s, 3H), 3.86 (m, 4H), 6.73 (d, 2H), 6.83 (d, 2H), 7.44 (m, 2H), 7.56 (m, 1H), 7.88 (d, 2H).

MS: 370 ($M + H^+$), 392 ($M + Na^+$).

Example 15

N-(5,7-Dimethoxy-benzothiazol-2-yl)-benzamide



1-Benzoyl-3-(3,5-dimethoxy-phenyl)-thiourea was treated in the same manner as in Example 7; yield 90 %.

MS: 315 ($M + H^+$).

Example 16

N-Naphtho[2,1-d]thiazol-2-yl-benzamide

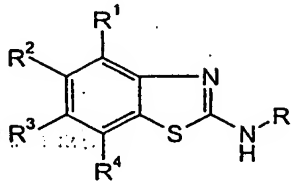
1-Benzoyl-3-naphthalen-2-yl-thiourea was treated in the same manner as in Example 7; yield 96 %.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ = 7.60 (m, 3H), 7.67 (m, 2H), 7.93 (d, 1H), 7.99 (d, 1H), 8.10 (m, 2H), 8.18 (m, 2H), 13.0 (bs, 1H).

MS: 305 ($M + H^+$).

Claims

1. A process for preparation of amino substituted benzothiazole derivatives of formula I



I

wherein

R^1, R^2 and R^3 are independently from each other hydrogen, lower alkyl, lower alkoxy or halogen;

R^4 is hydrogen, lower alkyl, lower alkyloxy, halogen, or is a five or six membered non aromatic heterocyclyl group, unsubstituted or substituted by lower alkyl or an oxo-group, or is $-NR^5R^6$, wherein R^5 and R^5 are independently from each other hydrogen, lower alkyl, -C(O)-lower alkyl, $-(CH_2)_nO$-lower alkyl or benzyl, opionally substituted by lower alkyl, or is a five or six membered heteroaryl group;

R^1 and R^2 or R^2 and R^3 may form together with the corresponding carbon atoms a ring containing $-O-CH_2-O-$ or $-CH=CH-CH=CH-$;

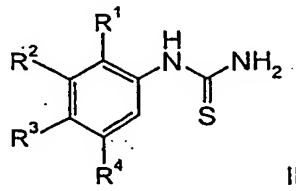
R is hydrogen or –C(O)R';

R' is a five or six membered non aromatic heterocyclyl group, five or six membered heteroaryl group or is aryl, which rings may be substituted by the groups, selected from lower alkyl, halogen-lower alkyl, lower alkoxy, cyano, nitro, -C(O)H, -C(O)OH or by pyrrolidin-1-yl-methyl;

n is 1 to 4;

and their pharmaceutically acceptable salts,

wherein the cyclization is carried out by the treatment of a compound of formula



II

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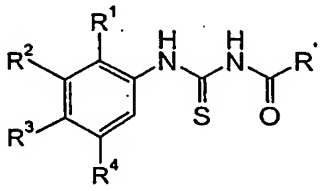
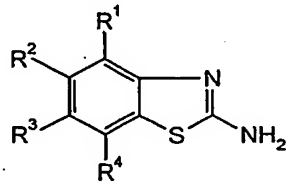


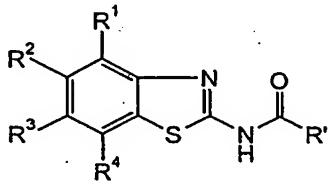
III

with sulphoxide/HBr/solvent to give the desired products of formula I for R is hydrogen (formula IA) and for R is –C(O)R' (formula IB)



IA

or



IB

2. The process in accordance with claim 1, wherein the sulphoxide is dimethyl sulphoxide.

3. The process in accordance with claim 1, wherein HBr is an *in situ* prepared bromide salt and a strong acid.

4. The process in accordance with claim 3, wherein the *in situ* prepared bromide salt and the strong acid is HBr-AcOH.

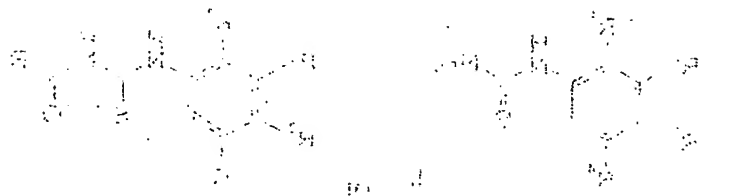
5. The process in accordance with claim 1, wherein the solvent is CH_2Cl_2, CH_3CN, THF, AcOH or EtOAc.

6. The process in accordance with claim 5, wherein the solvent is AcOH or EtOAc.

7. The process in accordance with claims 1, wherein a compound of formula II or III is suspended in a solvent and then treated with HBr and a sulphoxide.

8. The process in accordance with claim 7, wherein to a suspension of a compound of formula II or III in ethyl acetate or acetic acid is added hydrogen bromide in acetic acid and then dimethylsulfoxide is added.

9. The invention as herein before described.



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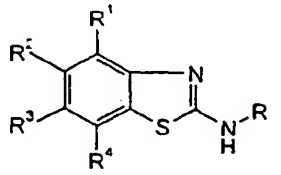
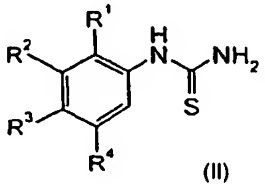
[Continued on next page]

(54) Title: CYCLIZATION PROCESS FOR SUBSTITUTED BENZOTHIAZOLE DERIVATIVES

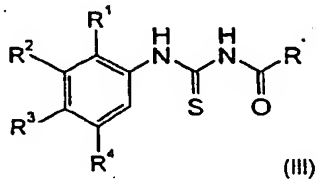


(I)

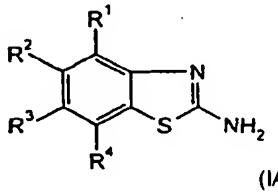


(II)

or

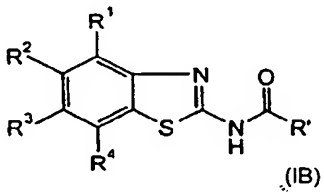


(III)



(IA)

or



(IB)

(57) Abstract: The present invention relates to a process for preparation of amino substituted benzothiazole derivatives of formula (I), wherein R^1, R^2 and R^3 are independently from each other hydrogen, lower alkyl, lower alkoxy or halogen; R^4 is hydrogen, lower alkyl, lower alkyloxy, halogen, or is a five or six membered non aromatic heterocyclyl group, unsubstituted or substituted by lower alkyl or an oxo-group, or is $-NR^5R^6$ wherein R^5 and R^6 are independently from each other hydrogen, lower alkyl, -C(O)-lower alkyl, $-(CH_2)_nO$-lower alkyl or benzyl, opionally substituted by lower alkyl, or is an five or six membered heteroaryl group; R^1 and R^2 or R^2 and R^3 may form together with the corresponding carbon atoms a ring containing $-O-CH_2-O-$ or -CH=CH-CH=CH-; R is hydrogen or -C(O)R'; R' is a five or six membered non aromatic heterocyclyl group, five or six membered heteroaryl group or is aryl, which rings may be substituted by the groups, selected from lower alkyl, halogen-lower alkyl, lower alkoxy, cyano, nitro, -C(O)H, -C(O)OH or by pyrrolidin-1-yl-methyl; n is 1 to 4; and to their pharmaceutically acceptable salts, wherein the cyclization is carried out by the treatment of a compound of formula with sulphoxide/HBr/solvent to give the desired products of formula (I) for R is hydrogen (formula IA) and for R is -C(O)R' (formula IB).

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PCT/EP 03/14928

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/82 C07D417/12 C07D417/04 C07D277/84

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 529 600 A (HOECHST AKTIENGESELLSCHAFT) 3 March 1993 (1993-03-03) cited in the application the whole document	1
A	BOGA C ET AL: "Condensation of thiourea derivatives with carbonyl compounds: one-pot synthesis of N-alkyl-1,3-thiazol-2-amines and of 3-alkyl-1,3-thiazolimines" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, 1999, pages 1363-1368, XP002296456 the whole document	1

☐ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2004	01/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Allard, M

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/14928

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 9
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 9

Claim 9 is so unclear (Article 6 PCT) with regard to the protection sought, that no meaningful search is possible for this claim, save the subject-matter already recited in claims 1-8.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/14928

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0529600 A	03-03-1993	DE 59207481 D1	12-12-1996
		EP 0529600 A1	03-03-1993
		JP 5194447 A	03-08-1993
		US 5374737 A	20-12-1994